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Cross-immunity between respiratory coronaviruses may limit COVID-19 fatalities

Ahmed Yaqinuddin

College of Medicine, Alfaisal University, Riyadh, Saudi Arabia

A B S T R A C T

Of the seven coronaviruses associated with disease in humans, SARS-CoV, MERS-CoV and SARS-CoV-2 cause considerable mortality but also share significant sequence homology, and potentially antigenic epitopes capable of inducing an immune response. The degree of similarity is such that perhaps prior exposure to one virus could confer partial immunity to another. Indeed, data suggests a considerable amount of cross-reactivity and recognition by the hosts immune response between different coronavirus infections. While the ongoing COVID-19 outbreak rapidly overwhelmed medical facilities of particularly Europe and North America, accounting for 78% of global deaths, only 8% of deaths have occurred in Asia where the outbreak originated. Interestingly, Asia and the Middle East have previously experienced multiple rounds of coronavirus infections, perhaps suggesting buildup of acquired immunity to the causative SARS-CoV-2 that underlies COVID-19. This article hypothesizes that a causative factor underlying such low morbidity in these regions is perhaps (at least in part) due to acquired immunity from multiple rounds of coronavirus infections and discusses the mechanisms and recent evidence to support such assertions. Further investigations of such phenomenon would allow us to examine strategies to confer protective immunity, perhaps aiding vaccine development.

Introduction

The ongoing global COVID-19 pandemic caused by the novel respiratory coronavirus SARS-CoV-2, first reported in Wuhan province in China [1], quickly spread around the world. On 11th March 2020, the World Health Organization (WHO) officially confirmed its status as a global pandemic [2], following which COVID-19 has gone on to underlie widespread global morbidity, with > 7.9 million confirmed infected cases, and > 400,000 directly linked fatalities as of 14th of June 2020 [3], with perhaps even more as an indirect consequence of this disease. However, while the outbreak rapidly overwhelmed medical facilities of particularly Europe and North America, only 9% of deaths have occurred in Asia where the outbreak originated, while Europe and North America account for 75% of case fatalities [3]. Perhaps a reasonable explanation could be a of diagnostic capabilities coupled with incomplete disclosure of information underlies such low reported number of deaths. However, this is at odds with the highly effective and supremely efficient healthcare systems present in South Korea, Japan and Singapore.

Perhaps recent history explains this, as many Asian countries have previously dealt with coronaviruses [4,5], including severe respiratory syndrome (SARS) caused by SARS-CoV which affected South Asian countries in 2002–2003 with 8000 human infections and a 10% case fatality rate [6,7]. Similarly, Middle East respiratory syndrome (MERS) caused by the MERS-CoV afflicted the Arabian Peninsula in 2012 [8], occurring mainly in the hospital outbreaks with significant mortality [9]. Alhamlan et al implied occurrence of a large number of asymptomatic cases which remained unaccounted [9], and also reported that only 3000 of the 4 million pilgrims who performed Hajj in 2013 were screened for MERS-CoV with no cases reported during the pilgrimage [10,11]. Anecdotal data from Saudi Arabia suggests that the majority of those performing both the Hajj and Umrah pilgrimages since 2012 return with mild to moderate respiratory illness, which usually takes longer than two weeks to resolve, suggesting perhaps exposure to circulating bouts of viral infections.

There are seven coronaviruses associated with disease in humans, which mostly amounts to mild respiratory illness. However, SARS-CoV, MERS-CoV and SARS-CoV-2 cause considerable mortality [12]. The acute lung injury seen in COVID-19 patients is perhaps due to a dysregulated innate immune response however, difference in case fatalities between different regions around the world could be due to difference in adaptive immune response due to prior exposure to coronaviruses [13,14]. Significantly, these three viruses (SARS-CoV, MERS-CoV and SARS-CoV-2) also share significant sequence homology, potentially sharing antigenic epitopes capable of inducing an adaptive immune response. To this degree, perhaps prior exposure to one virus could confer partial immunity to another. Thus, as the majority of Asian/Middle Eastern populations have experiences repeated exposure to multiple rounds of coronavirus infections, this has perhaps facilitated the buildup of an adaptive immune response to SAR-CoV-2 exposure. This adaptive immune response could be one of the reasons for low death rates seen in this region.

E-mail address: ayaqinuddin@alfaisal.edu.

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Evaluation of hypothesis

Before SARS-CoV, only two human coronaviruses (HCoV-229E and HCoVOC43) were known to cause mild respiratory infections and associated mortality [12,15]. In 2004/2005, two additional CoVs were identified including HCoV-NL63 and HCoV-HKU1, respectively [16,17]. Collectively these four CoVs are thought to underlie 15–30% of the common colds seen globally; possibly also causing severe lower respiratory tract infections in elderly and immunocompromised patients [18–20]. Typically, all coronaviruses are spherical in structure, consisting of transmembrane trimeric spike (S) glycoproteins, [21], an abundant membrane (M) glycoprotein, and transmembrane envelope (E) protein [21]. Finally, the RNA of the CoVs is bound to the nucleocapsid (N) protein in a manner resembling string-on-beads [21]. Sequence analysis of SARS-CoV-2, SARS-CoV, SARS like bat viruses, and MERS-CoV indicated high sequence homology between S, M, E and N proteins, while SARS-CoV-2 is remarkably similar to SARS-CoV at the amino acid level [22].

T cells contain specific receptors (TCRs) which are used to identify cognate antigens. The type 1 Major histocompatibility complexes (MHC) present antigenic peptides to T cells [23], while MHC II complexes can present larger peptides. While T cells naturally contain a pool of approximately 10^8 TCRs, the number of antigenic peptides presented by MHCs exceeds 10^{15} [23,24]. Furthermore, a single TCR can recognize > million peptides presented by one MHC, suggesting a considerable amount of cross-reactivity and recognition by TCRs of different antigenic proteins [25]. Indeed, cross reactivity is common among peptides with have sequence homology; but also between peptides with non-homologous sequences [26–28]. In the case of MHC I, TCR cross-reactivity is demonstrated between peptides of the same length, while non-homologous peptide sequences can be recognized by TCRs via hotspot recognition [29].

Plasma and B cells also produce antibodies that bind to toxins and antigens to neutralize them. Such antigen binding occurs at the fragment antigen binding (Fab) site. All antibodies are polyspecific, as their binding sites consist of several paratopes corresponding to several B-cell epitopes on antigens [30]. On average, 15 amino acids form B-cell epitopes that are mainly conformational or discontinuous and their recognition is hotspot based [31]. $CD8^+$ T cells are cytotoxic, capable of attacking and killing viruses, while $CD4^+$ T cells activate B-cells and plasma cells to produce antibodies against infecting agents [32]. Indeed, 80% of infiltrative cells following CoV infection in the lung interstitium following CoV infection are $CD8^+$ T cells, that are thought to be responsible for inflammatory damage to the lung [33]. In MERS-CoV infection, the T-cell response is considered more important in controlling the infection as compared to the B-cell response [34]. Indeed, in T-cell deficient mouse models, T-cells can survive and kill virus infected cells [34], while a decrease in MERS-CoV infection corresponded to cross-reactivity of T-cell response [35].

SARS-CoV infection is characterized by depletion of $CD8^+$ T cells which culminates in immune mediated interstitial pneumonitis and acute lung injury. However, this depletion is not associated with viral replication at the time of SAR-CoV infection [36,37]. In fact, reduced T-cell recruitment and decreased antibody and cytokine production during SARS-CoV infection is attributed to depletion of $CD4^+$ T cells. MERS-CoV and SARS-CoV infection activates apoptotic pathways within T-cells, culminating in prolonged infection and increased viral survival [38,39]. Interestingly, patients recovering from SARS-CoV seemed to exhibit a 'memory' of T-cell responses against viral structural proteins (S, M and N), that can last as long as 11 years [32]. This suggests a persistent long-term immune response against viral structural proteins which share sequence homology between SARS-CoV and SARS-CoV-2, opening doors for a common vaccine development for SARS- like viruses.

Consequences of the hypothesis

Comparative analysis of B-cell and T-cell epitopes between SARS-CoV and SAR-CoV-2 using the Immune Epitope Database and Analysis Resource (IEDB) showed a high degree of homology between the two viruses [40]. Grifoni et al recently demonstrated between SARS-CoV to SARS-CoV-2 that out of 6/10 regions exhibited > 90% homology, while 2/10 have 80–89% identical sequences [40]. Additionally, T cell epitopes for N and M proteins are most conserved between SARS-CoV and SARS-CoV-2 [40]. In a recent study, investigators used HLA predicted peptide pools to identify circulating SARS-CoV-2 specific $CD4^+$ and $CD8^+$ T cells in convalescent COVID-19 patients [41], finding reactive CD4 + T cells in 40–60% of healthy controls, demonstrating cross-reactive T cell recognition in individuals previously exposed to coronaviruses like SARS-CoV-2 [41].

Anderson et al used convalescent SARS sera to neutralize SARS-CoV-2 [42], demonstrating cross-neutralization of SARS-CoV-2 by neutralizing antibodies produced against SARS-CoV. Importantly, these neutralizing antibodies persisted for 9–17 years [42], further demonstrating long term immunity against SARS-CoV. Intriguingly, the neutralizing antibodies against the N protein of the two viruses was indistinguishable, suggesting of cross reactivity of antibodies against viral antigens [42].

It thus seems obvious that there is a high degree of cross-reactivity between T and B cell epitopes of SARS-CoV-2 and other SARS-like viruses [41], which is also observed between antibodies produced against the relevant viral structural proteins [43]. Perhaps the comparative lack of serious cases of COVID-19 in locations where SARS-like infections have been prevalent is due to partial immunity conferred from cross reactivity of B and T cell epitopes and antibodies. To assess this hypothesis B and T cells epitopes and antibodies against SARS like viruses need to be assessed in convalescent COVID-19 patients with mild, moderate, and severe disease. Finally, longevity of SARS-CoV-2 antibodies need to be assessed to attain a better understanding of protective immunity and vaccine development.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.110049.

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